

WHAT IS CLAIMED IS:

1. A method of treating hypersecretion of mucus, comprising administering, topically to the airways of a patient in need thereof, a therapeutically effective amount of a compound, said compound comprising:-

(a) a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin, which L-chain or L-chain fragment includes the active proteolytic enzyme domain of the L-chain;

(b) a targeting domain that binds to a target cell selected from the group consisting of (i) a mucus secreting cell, and (ii) a neuronal cell controlling or directing mucus secretion; and

(c) a translocating domain that translocates the L-chain or L-chain fragment into the target cell;

with the proviso that said compound is not a botulinum toxin; and wherein, following administration to said patient, the compound binds to and delivers the L-chain or L-chain fragment into said target cell, thereby (i) inhibiting mucus secretion by mucus secreting cells, (ii) inhibiting neurotransmitter release from neuronal cells controlling or directing mucus secretion, or (iii) inhibiting mucus secretion by mucus secreting cells and inhibiting neurotransmitter release from neuronal cells controlling or directing mucus secretion.

2. A method according to Claim 1, wherein said translocating domain is a translocating domain of a microbial protein.

3. A method according to Claim 1, wherein said translocating domain is a translocating domain of a bacterial or viral protein.

4. A method according to Claim 1, wherein said translocating domain is a translocating domain of a bacterial toxin, or a translocating domain of a virally expressed membrane fusion protein.

5. A method according to Claim 1, wherein said translocating domain is selected from the group consisting of a translocating domain of diphtheria toxin, domain II of pseudomonas exotoxin A, a translocating domain of influenza virus haemagglutinin, a translocating domain of a fusogenic protein

of Semliki Forest virus, a translocating domain of vesicular stomatitis virus glycoprotein G, a translocating domain of SER virus F protein and a translocating domain of Foamy virus envelope glycoprotein.

6. A method according to Claim 1, wherein the targeting domain is a domain selected from the group consisting of Substance P, vasoactive intestinal polypeptide (VIP), beta₂ adrenoreceptor agonists, gastrin releasing peptide, and calcitonin gene related peptide.

7. A method according to Claim 1, wherein said targeting domain binds to a target cell selected from the group consisting of epithelial goblet cells, submucosal gland mucus-secreting cells, Clara cells, serous cells, sensory efferent C-fibres, and Non-adrenergic Non-Cholinergic neural system fibres.

8. A method of treating chronic obstructive pulmonary disease (COPD), comprising administering, topically to the airways of a patient in need thereof, a therapeutically effective amount of a compound, said compound comprising:-

(a) a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin, which L-chain or L-chain fragment includes the active proteolytic enzyme domain of the L-chain;

(b) a targeting domain that binds to a target cell selected from the group consisting of (i) a mucus secreting cell, and (ii) a neuronal cell controlling or directing mucus secretion; and

(c) a translocating domain of that translocates the L-chain or L-chain fragment into the target cell;

with the proviso that said compound is not a botulinum toxin; and

wherein following administration to said patient the compound binds to and delivers the L-chain or L-chain fragment into said target cell, thereby (i) inhibiting mucus secretion by mucus secreting cells, (ii) inhibiting neurotransmitter release from neuronal cells controlling or directing mucus secretion, or (iii) inhibiting mucus secretion by mucus secreting cells and inhibiting neurotransmitter release from neuronal cells controlling or directing mucus secretion.

9. A method according to Claim 8, wherein said translocating domain is a translocating domain of a microbial protein.

10. A method according to Claim 8, wherein said translocating domain is a translocating domain of a bacterial or viral protein.

11. A method according to Claim 8, wherein said translocating domain is a translocating domain of a bacterial toxin, or a translocating domain of a virally expressed membrane fusion protein.

12. A method according to Claim 8, wherein said translocating domain is selected from the group consisting of a translocating domain of diphtheria toxin, domain II of pseudomonas exotoxin A, a translocating domain of influenza virus haemagglutinin, a translocating domain of a fusogenic protein of Semliki Forest virus, a translocating domain of vesicular stomatitis virus glycoprotein G, a translocating domain of SER virus F protein and a translocating domain of Foamy virus envelope glycoprotein.

13. A method according to Claim 8, wherein the targeting domain is a domain selected from the group consisting of Substance P, VIP, beta₂ adrenoreceptor agonists, gastrin releasing peptide, and calcitonin gene related peptide.

14. A method according to Claim 8, wherein said targeting domain selectively binds to a target cell selected from the group consisting of epithelial goblet cells, submucosal gland mucus-secreting cells, Clara cells, and serous cells.

15. A method for treating asthma, comprising administering, topically to the airways of a patient in need thereof, a therapeutically effective amount of a compound, said compound comprising:-

(a) a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin, which L-chain or L-chain fragment includes the active proteolytic enzyme domain of the L-chain;

(b) a targeting domain that binds to a target cell selected from the group consisting of (i) a mucus secreting cell, and (ii) a neuronal cell controlling or directing mucus secretion; and

(c) a translocating domain that translocates the L-chain or L-chain fragment into the target cell;

with the proviso that said compound is not a botulinum toxin; and wherein following administration to said patient the compound binds to and delivers the L-chain or L-chain fragment into said target cell, thereby (i) inhibiting mucus secretion by mucus secreting cells, (ii) inhibiting neurotransmitter release from neuronal cells controlling or directing mucus secretion, or (iii) inhibiting mucus secretion by mucus secreting cells and inhibiting neurotransmitter release from neuronal cells controlling or directing mucus secretion.

16. A method according to Claim 15, wherein said translocating domain is a translocating domain of a microbial protein.

17. A method according to Claim 15, wherein said translocating domain is a translocating domain of a bacterial or viral protein.

18. A method according to Claim 15, wherein said translocating domain is a translocating domain of a bacterial toxin, or a translocating domain of a virally expressed membrane fusion protein.

19. A method according to Claim 15, wherein said translocating domain is selected from the group consisting of a translocating domain of diphtheria toxin, domain II of pseudomonas exotoxin A, a translocating domain of influenza virus haemagglutinin, a translocating domain of a fusogenic protein of Semliki Forest virus, a translocating domain of vesicular stomatitis virus glycoprotein G, a translocating domain of SER virus F protein and a translocating domain of Foamy virus envelope glycoprotein.

20. A method according to Claim 15, wherein the targeting domain is a domain selected from the group consisting of Substance P, VIP, beta₂ adrenoreceptor agonists, gastrin releasing peptide, and calcitonin gene related peptide.

21. A method according to Claim 15, wherein said targeting domain selectively binds to a target cell selected from the group consisting of epithelial goblet cells, submucosal gland mucus-secreting cells, Clara cells, and serous cells.

22. A compound which inhibits mucus secretion by mucus secreting cells, said compound comprising:-

(a) a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin, which L-chain or L-chain fragment includes the active proteolytic enzyme domain of the L-chain;

(b) a targeting domain that selectively binds to a target cell that is a mucus secreting cell; and

(c) a translocating domain that translocates the L-chain or L-chain fragment into the target cell;

with the proviso that said compound is not a botulinum toxin.

23. A compound according to Claim 22, wherein said translocating domain is a translocating domain of a microbial protein.

24. A compound according to Claim 22, wherein said translocating domain is a translocating domain of a bacterial or viral protein.

25. A compound according to Claim 22, wherein said translocating domain is a translocating domain of a bacterial toxin, or a translocating domain of a virally expressed membrane fusion protein.

26. A compound according to Claim 22, wherein said translocating domain is selected from the group consisting of a translocating domain of diphtheria toxin, domain II of pseudomonas exotoxin A, a translocating domain of influenza virus haemagglutinin, a translocating domain of a fusogenic protein of Semliki Forest virus, a translocating domain of vesicular stomatitis virus glycoprotein G, a translocating domain of SER virus F protein and a translocating domain of Foamy virus envelope glycoprotein.

27. The compound according to Claim 22, wherein the targeting domain is a domain selected from the group consisting of Substance P, VIP, beta₂

adrenoreceptor agonists, gastrin releasing peptide, and calcitonin gene related peptide.

28. The compound according to Claim 22, wherein said targeting domain selectively binds to a target cell selected from the group consisting of epithelial goblet cells, submucosal gland mucus-secreting cells, Clara cells, and serous cells.

29. A compound according to Claim 22, wherein said targeting domain binds to (i) a mucus secreting cell, but not to (ii) a neuronal cell controlling or directing mucus secretion.

30. A compound according to Claim 29, wherein the targeting domain is a domain selected from the group consisting of Substance P, VIP, beta₂ adrenoreceptor agonists, gastrin releasing peptide and calcitonin gene related peptide.

31. A compound according to Claim 29, wherein said targeting domain binds to a target cell selected from the group consisting of epithelial goblet cells, submucosal gland mucus-secreting cells, Clara cells, and serous cells.

32. A pharmaceutical composition for topical administration to airways of a patient suffering from mucus hypersecretion, comprising:-

- (a) an amount of a compound, effective to inhibit mucus hypersecretion, wherein the compound comprises:-
 - (i) a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin, which L-chain or L-chain fragment includes the active proteolytic enzyme domain of the L-chain;
 - (ii) a targeting domain that selectively binds to a target cell that is a mucus secreting cell; and
 - (iii) a translocating domain that translocates the L-chain or L-chain fragment into the target cell;

with the proviso that said compound is not a botulinum toxin; and

- (b) a formulation component selected from the group consisting of an excipient, an adjuvant and a propellant;

wherein the composition is for nasal or oral administration of the compound to a patient.

33. A pharmaceutical composition according to Claim 32, wherein said translocating domain is a translocating domain of a microbial protein.

34. A pharmaceutical composition according to Claim 32, wherein said translocating domain is a translocating domain of a bacterial or viral protein.

35. A pharmaceutical composition according to Claim 32, wherein said translocating domain is a translocating domain of a bacterial toxin, or a translocating domain of a virally expressed membrane fusion protein.

36. A pharmaceutical composition according to Claim 32, wherein said translocating domain is selected from the group consisting of a translocating domain of diphtheria toxin, domain II of pseudomonas exotoxin A, a translocating domain of influenza virus haemagglutinin, a translocating domain of a fusogenic protein of Semliki Forest virus, a translocating domain of vesicular stomatitis virus glycoprotein G, a translocating domain of SER virus F protein and a translocating domain of Foamy virus envelope glycoprotein.

37. A pharmaceutical composition according to Claim 32, wherein the targeting domain is a domain selected from the group consisting of Substance P, VIP, beta₂ adrenoreceptor agonists, gastrin releasing peptide, and calcitonin gene related peptide.

38. A pharmaceutical composition according to Claim 32, wherein said targeting domain selectively binds to a target cell selected from the group consisting of epithelial goblet cells, submucosal gland mucus-secreting cells, Clara cells, and serous cells.

39. A pharmaceutical composition according to Claim 32, in a formulation for aerosol administration.

40. A method of manufacture of a compound according to Claim 22, comprising:-

- (a) obtaining a clostridial neurotoxin and removing or disabling the native target cell binding domain (H_C) and native translocation domain (H_N) of said clostridial neurotoxin to produce a modified clostridial neurotoxin or
- (b) obtaining a modified clostridial neurotoxin that has had the native target cell binding domain (H_C) and the native translocation domain (H_N) removed or disabled; and
- (c) linking the modified neurotoxin with:-
 - (i) a targeting domain that selectively binds the compound to a mucus secreting cell, and
 - (ii) a translocating domain that translocates the L-chain or L-chain fragment into the target cell.

41. A method according to Claim 40, wherein said translocating domain is a translocating domain of a microbial protein.

42. A method according to Claim 40, wherein said translocating domain is a translocating domain of a bacterial or viral protein.

43. A method according to Claim 40, wherein said translocating domain is a translocating domain of a bacterial toxin, or a translocating domain of a virally expressed membrane fusion protein.

44. A method according to Claim 40, wherein said translocating domain is selected from the group consisting of a translocating domain of diphtheria toxin, domain II of pseudomonas exotoxin A, a translocating domain of influenza virus haemagglutinin, a translocating domain of a fusogenic protein of Semliki Forest virus, a translocating domain of vesicular stomatitis virus glycoprotein G, a translocating domain of SER virus F protein and a translocating domain of Foamy virus envelope glycoprotein.

45. A method according to Claim 40, wherein the targeting domain is a domain selected from the group consisting of Substance P, VIP, beta₂ adrenoreceptor agonists, gastrin releasing peptide, and calcitonin gene related peptide.

46. A method according to Claim 40, wherein said targeting domain selectively binds to a target cell selected from the group consisting of epithelial goblet cells, submucosal gland mucus-secreting cells, Clara cells, and serous cells.

47. A method of manufacture of a compound according to Claim 22, comprising linking together:

(a) a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin, which L-chain or L-chain fragment includes the active proteolytic enzyme domain of the L-chain;

(b) a translocating domain that translocates the L-chain or L-chain fragment into the target cell; and

(c) a targeting domain that selectively binds the compound to a mucus secreting cell.

48. A method according to Claim 47, wherein said translocating domain is a translocating domain of a microbial protein.

49. A method according to Claim 47, wherein said translocating domain is a translocating domain of a bacterial or viral protein.

50. A method according to Claim 47, wherein said translocating domain is a translocating domain of a bacterial toxin, or a translocating domain of a virally expressed membrane fusion protein.

51. A method according to Claim 47, wherein said translocating domain is selected from the group consisting of a translocating domain of diphtheria toxin, domain II of pseudomonas exotoxin A, a translocating domain of influenza virus haemagglutinin, a translocating domain of a fusogenic protein of Semliki Forest virus, a translocating domain of vesicular stomatitis virus glycoprotein G, a translocating domain of SER virus F protein and a translocating domain of Foamy virus envelope glycoprotein.

52. A method according to Claim 47, wherein the targeting domain is a domain selected from the group consisting of Substance P, VIP, beta₂

adrenoreceptor agonists, gastrin releasing peptide, and calcitonin gene related peptide.

53. A method according to Claim 47, wherein said targeting domain selectively binds to a target cell selected from the group consisting of epithelial goblet cells, submucosal gland mucus-secreting cells, Clara cells, and serous cells.

54. A method according to Claim 47, further comprising formulating the compound in a nasally or orally administrable composition in combination with a formulation component selected from the group consisting of an excipient, an adjuvant and a propellant, wherein said composition is for topical administration to airways of a patient.